

**WHAT IS CLAIMED IS:**

1. An isolated peptide comprising the formula:  $X_1X_2X_3X_4X_5X_6X_7X_8$  (SEQ ID NO: 32), wherein  $X_1$  through  $X_8$  are amino acid residues, wherein said peptide binds to VEGFR3, and wherein

5 the amino acid residue at  $X_1$  is a glycine residue or a conservative substitution thereof;

the amino acid residue at  $X_2$  is a tyrosine residue or a conservative substitution thereof;

10 the amino acid residue at  $X_3$  is a tryptophan residue or a conservative substitution thereof;

the amino acid residue at  $X_4$  is a leucine residue or a conservative substitution thereof;

the amino acid residue at  $X_5$  is a threonine residue or a conservative substitution thereof;

15 the amino acid residue at  $X_6$  is an isoleucine residue or a conservative substitution thereof;

the amino acid residue at  $X_7$  is a tryptophan residue or a conservative substitution thereof; and

20 the amino acid residue at  $X_8$  is a glycine residue or a conservative substitution thereof.

2. An isolated peptide according to claim 1, further comprising amino- and carboxy-terminal cysteine residues.

25 3. An isolated peptide according to claim 1, comprising an amino acid sequence of the formula:  $CX_1X_2X_3X_4X_5X_6X_7X_8C$  (SEQ ID NO: 33).

30 4. The isolated peptide according to any one of claims 1-3, wherein the conservative substitution at position  $X_1$  is selected from the group consisting of isoleucine, valine, leucine, alanine, cysteine, phenylalanine, proline, tryptophan, tyrosine, norleucine and methionine.

5. The isolated peptide according to any one of claims 1-4, wherein the conservative substitution at position  $X_2$  is selected from the group consisting of isoleucine, valine, leucine, alanine, cysteine, glycine, phenylalanine, proline, tryptophan, norleucine and methionine.
- 5
6. The isolated peptide according to any one of claims 1-5, wherein the conservative substitution at position  $X_3$  is selected from the group consisting of isoleucine, valine, leucine, alanine, cysteine, glycine, phenylalanine, proline, tyrosine, norleucine and methionine.
- 10
7. The isolated peptide according to any one of claims 1-6, wherein the conservative substitution at position  $X_4$  is selected from the group consisting of isoleucine, valine, alanine, cysteine, glycine, phenylalanine, proline, tryptophan, tyrosine, norleucine and methionine.
- 15
8. The isolated peptide of any one of claims 1 through 7, wherein the conservative substitution at position  $X_5$  is selected from the group consisting of asparagine, glutamine, and serine.
- 20
9. The isolated peptide of any one of claims 1 through 9, wherein the conservative substitution at position  $X_6$  is selected from the group consisting of valine, leucine, alanine, cysteine, glycine, phenylalanine, proline, tryptophan, tyrosine, norleucine or methionine.
- 25
10. The isolated peptide of any one of claims 1 through 9, wherein the conservative substitution at position  $X_7$  is selected from the group consisting of isoleucine, valine, leucine, alanine, cysteine, glycine, phenylalanine, proline, tyrosine, norleucine and methionine.

11. The isolated peptide of any one of claims 1 through 10, wherein the conservative substitution at position  $X_8$  is selected from the group consisting of isoleucine, valine, leucine, alanine, cysteine, phenylalanine, proline, tryptophan, tyrosine, norleucine and methionine.

5

12. An isolated peptide according to claim 1, comprising the sequence  $Y_1$ GYWLTIWGY $_2$  (SEQ ID NO: 34), wherein  $Y_1$  and  $Y_2$  are amino acids.

10

13. The isolated peptide of claim 1, wherein said peptide comprises the sequence CGYWLTIWGC (SEQ ID NO: 35).

15

14. An isolated peptide comprising an amino acid sequence selected from the group consisting of: SGYWWD TWF (SEQ ID NO: 36), SCYWRD TWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID NO: 38), FVGWTKVLG (SEQ ID NO: 39), YSSSMRWRH (SEQ ID NO: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID NO: 42), WFSASLRFR (SEQ ID NO: 43), and conservative substitution-analogs thereof, wherein said peptide binds human VEGFR-3.

20

15. An isolated peptide comprising an amino acid sequence selected from the group consisting of: SGYWWD TWF (SEQ ID NO: 36), SCYWRD TWF (SEQ ID NO: 37), KVGWSSPDW (SEQ ID NO: 38), FVGWTKVLG (SEQ ID NO: 39), YSSSMRWRH (SEQ ID NO: 40), RWRGNAYPG (SEQ ID NO: 41), SAVFRGRWL (SEQ ID NO: 42), WFSASLRFR (SEQ ID NO: 43), wherein said peptide binds human VEGFR-3.

25

16. An isolated peptide comprising an amino acid sequence selected from the group consisting of: WQLGRNWI (SEQ ID NO: 44), VEVQITQE (SEQ ID NO: 45), AGKASSLW (SEQ ID NO: 46), RALDSALA (SEQ ID NO: 47), YGFEEAAW (SEQ ID NO: 48), YGFLWGM (SEQ ID NO: 49), SRWRILG (SEQ ID NO: 50), HKWQKRQ (SEQ ID NO: 51), MDPWGGW (SEQ ID NO: 52), RKVWDIR (SEQ ID NO: 53), VWDHGV (SEQ ID NO: 54), and conservative substitution-analogs thereof, wherein said peptide binds human VEGFR-3.

30

17. A peptide comprising an amino acid sequence selected from the group consisting of: WQLGRNWI (SEQ ID NO: 44), VEVQITQE (SEQ ID NO: 45), AGKASSLW (SEQ ID NO: 46), RALDSALA (SEQ ID NO: 47), YGFEAAW (SEQ ID NO: 48), YGFLWGM (SEQ ID NO: 49), SRWRILG (SEQ ID NO: 50), HKWQKRQ (SEQ ID NO: 51), MDPWGGW (SEQ ID NO: 52), RKVWDIR (SEQ ID NO: 53), VWDHGV (SEQ ID NO: 54), wherein said peptide binds human VEGFR-3.

18. An isolated peptide according to any one of claims 14-17, further comprising amino- and carboxy-terminal cysteine residues.

19. An isolated peptide that binds VEGFR-3, comprising an amino acid sequence selected from the group consisting of: CWQLGRNWIC (SEQ ID NO: 55), CVEVQITQEC (SEQ ID NO: 56), CAGKASSLWC (SEQ ID NO: 57), CRALDSALAC (SEQ ID NO: 58), CYGFEAAWC (SEQ ID NO: 59), CYGFLWGMC (SEQ ID NO: 60), CSRWRILGC (SEQ ID NO: 61), CHKWQKRQC (SEQ ID NO: 62), CMDPWGGWC (SEQ ID NO: 63), CRKVWDIRC (SEQ ID NO: 64), CVWDHGVC (SEQ ID NO: 65).

20. An isolated peptide that binds VEGFR-3, comprising the amino acid sequence CGQMCTVWCSSGC (SEQ ID NO: 66).

21. An isolated peptide comprising the amino acid sequence  $GYWX_1X_2X_3W$  (SEQ ID NO: 67), wherein  $X_1$ ,  $X_2$ , and  $X_3$  comprise amino acids, and wherein the peptide binds VEGFR-3.

22. An isolated peptide according to claim 21, comprising the amino acid sequence  $GYWX_1X_2X_3WX_4$  (SEQ ID NO: 68), wherein  $X_4$  comprises an amino acid.

23. An isolated peptide according to claim 21 or 22, further comprising amino- and carboxy-terminal cysteine residues.

24. An isolated peptide according to any one of claims 1-23, wherein said peptide further comprises an intramolecular bond between amino acid residues to form a cyclic peptide.

5 25. An isolated peptide according to claim 24, wherein the peptide comprises amino- and carboxy-terminal cysteines, and the intramolecular bond comprises a disulfide bond between the cysteines.

10 26. An isolated peptide according to any one of claims 1-25, wherein said peptide inhibits Vascular Endothelial Growth Factor C (VEGF-C) binding to VEGFR-3.

27. An isolated peptide according to any one of claims 1-26, further comprising a cytotoxic agent attached to the peptide.

15 28. A peptide according to claim 27, wherein the cytotoxic agent comprises a radioisotope.

29. A peptide according to claim 27, wherein the cytotoxic agent comprises an anti-neoplastic pro-drug.

20

30. A chimeric protein comprising a therapeutic protein amino acid sequence attached to the amino acid sequence of a peptide according to any one of claims 1-26.

25

31. A chimeric protein according to claim 30, wherein the therapeutic protein comprises a tumor necrosis factor.

32. A peptide according to any one of claims 1-26 attached to an antibody or fragment thereof.

33. The isolated peptide of any of claims 1 through 26, wherein said peptide further comprises a modification to increase the circulating *in-vivo* half-life of the peptide in a mammal.

5 34. A peptide dimer comprising first and second peptide monomers, wherein at least one of the peptide monomers comprises a peptide according to any one of claims 1-33, and wherein the dimer binds to VEGFR-3.

10 35. A peptide dimer according to claim 34, wherein the first and second peptide monomer comprise peptides according to any one of claims 1-25.

36. A peptide dimer according to claim 35, wherein the first and second monomers comprise the same peptide.

15 37. The isolated peptide or peptide dimer according to any one of claims 1-36, wherein said peptide or dimer further binds to at least one growth factor receptor selected from the group consisting of VEGFR-1, VEGFR-2 and neuropilin-1 (NP-1) and neuropilin-2 (NP-2).

20 38. A composition comprising an isolated peptide or peptide dimer according to any one of claims 1 through 37 in a pharmaceutically acceptable carrier.

25 39. A method of inhibiting the proliferation of a cell comprising contacting a cell that expresses VEGFR-3 with a peptide according to any one of claims 1 through 33 in an amount effective to inhibit the proliferation of said cell.

40. The method of claim 39, wherein said cell is an endothelial cell or endothelial progenitor cell.

30 41. The method of claim 39, wherein said cell is a lymphatic endothelial cell.

42. The method of claim 39, wherein said cell is a mammalian hematopoietic progenitor cell.

5 43. The method of claim 39, wherein said contacting comprises contacting said cell with a composition comprising said peptide in a pharmaceutically acceptable carrier.

10 44. A method for inhibiting proliferation of a cell that expresses VEGFR-3, comprising a step of contacting the cell with a nucleic acid comprising a nucleotide sequence encoding the peptide and further comprising a promoter active in said cell, wherein said promoter is operably linked to the nucleotide sequence encoding said peptide, under conditions permitting the uptake of said nucleic acid and expression of said peptide by said cell in an amount effective to inhibit the proliferation of said cell.

15 45. The method of claim 44, wherein said nucleic acid is encapsulated in a liposome.

20 46. The method of claim 44, wherein said nucleic acid is a viral vector selected from the group consisting of retrovirus, adenovirus, adeno-associated virus, vaccinia virus and herpesvirus.

47. The method of any one of claims 39-46, wherein said cell is contacted *in vitro*.

48. The method of any one of claims 39-46, wherein said cell is contacted *in vivo*.

25 49. A method of treating a mammalian subject to modulate the growth in said subject of cells that express VEGFR-3, comprising administering to the mammalian subject a composition comprising a peptide according to any one of claims 1 through 33.



50. A method according to claim 49, wherein the mammalian subject has been diagnosed with a disease characterized by proliferation of endothelial cells that express VEGFR-3.

5 51. A method according to claim 50, wherein the disease comprises a tumor characterized by blood vessel or lymphatic vessel neovascularization, and wherein the neovascularization comprises endothelial cells that express VEGFR-3.

10 52. A method according to claim 50, wherein the disease comprises a cancer wherein the cancer cells express VEGFR-3.

15 53. A method according to claim 50, wherein the disease comprises a cancer wherein the cancer cells express a VEGFR-3 ligand selected from VEGF-C and VEGF-D.

20 54. A method of inhibiting metastatic spread of a cancer in a mammalian subject comprising administering to a mammalian subject suspected of having cancer a peptide according to any one of claims 1-33, in an amount effective to inhibit metastatic spread of said cancer.

25 55. A method for treating cancer comprising administering to a mammalian subject diagnosed with a cancer a composition comprising a peptide according to any one of claims 1-33, in an amount effect to reduce growth or neoplastic spread of the cancer.

30 56. The method according to any one of claims 49-55, wherein the subject is a human.

57. The method according to any one of claims 51-56, wherein said peptide inhibits at least one of angiogenesis and lymphangiogenesis near the cancer in said subject.



58. The method according to any one of claims 51-56, wherein said cancer is breast cancer.

59. A method of treating a mammalian subject having a disease characterized by proliferation of cells that express at least one of VEGFR-3, VEGF-C, and VEGF-D, comprising a step of administering to the subject a nucleic acid comprising a nucleotide sequence encoding a peptide according to any one of claims 1-33 and further comprising a promoter, wherein said promoter is operably linked to the nucleotide sequence encoding said peptide.

60. A method according to any one of claims 49-59, further comprising a step of administering to the subject a second cancer therapeutic agent.

61. The method of claim 60, wherein said second cancer therapeutic agent comprises a chemotherapeutic agent, a radioactive agent, a nucleic acid encoding a cancer therapeutic agent and anti-lymphangiogenic agent or an anti-angiogenic agent.

62. A method according to any one of claims 39-61, wherein the subject has been diagnosed with an operable tumor, and wherein the administering step is performed before, during, or after the tumor is resected.

63. A method according to any one of claims 49-63, wherein the subject has a cancer of a tissue, organ, or cell selected from the group consisting of brain, lung, liver, spleen, kidney, lymph node, small intestine, blood cells, pancreas, colon, stomach, breast, endometrium, prostate, testicle, ovary, skin, head and neck, esophagus, bone marrow and blood.

64. A method of treating a pathology characterized by VEGFR-3 binding to a natural ligand that binds VEGFR-3, comprising the step of administering to an individual in need thereof a peptide according to any one of claims 1 through 33.

65. A method of screening a biological sample for VEGFR-3, comprising steps of:  
a) contacting a biological sample suspected of containing VEGFR-3 protein  
with a composition comprising a peptide according to any one of claims 1 through 33;  
and  
5 b) determining the binding of said peptide with said receptor.

66. A method according to claim 65, wherein the peptide comprises a detectable  
label, and the determining step comprises detecting the presence of the label bound to  
the biological sample.

67. A method according to claim 65 or 66, wherein the biological sample comprises  
mammalian cells, and the determining step comprising determining the presence or  
quantity of peptide bound to the cells.

68. A method of imaging cells that express VEGFR-3 in a tissue suspected of  
containing cells that express VEGFR-3 comprising:  
a) contacting the tissue with a composition comprising a peptide of any one  
of claims 1 through 33; and  
b) imaging cells that express VEGFR-3 in said tissue by detecting said  
peptide bound to cell in said tissue.

69. The method of claim 68, wherein said peptide comprises a detectable label, and  
wherein the imaging step comprises detecting the label in the tissue.

70. The method of claim 68 or 69, wherein said tissue is human tissue.

71. The method of claim 70, wherein said tissue is neoplastic tissue.

72. A method of screening for neovascularization in a tumor, comprising steps of:  
contacting a tissue suspected of containing a tumor with a peptide according to  
any one of claims 1-33; and

detecting binding of the peptide in the tissue, wherein binding of the peptide to the tissue correlates with the presence of neovascularization in the tissue.

5 73. A method according to claim 72, wherein the peptide comprises a label, and the detecting step comprises measuring the quantity and/or distribution of the label.

74. A method of diagnosing a cancer, comprising screening for neovascularization according to claim 73, wherein increased quantity and/or distribution of the label correlates with increased neovascularization and increased aggressiveness of the tumor.